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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/286,166	04/05/1999	DANA M. FOWLKES	CPI-012CP4BC	4623

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EXAMINER
BRANNOCK, MICHAEL T

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 07/03/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/286,166	Fowlkes, DM et al.
Examiner	**Art Unit**
Michael Brannock, Ph.D	1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 14, 2002*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *43-58* is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *43-58* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application: Claims and Amendments

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/14/02 has been entered.

2. Claims 43-58 are pending

Maintained Rejections:

Double Patenting

3. Claims 43-51 stand and new claims 52-58 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-47 of U.S. Patent No. 6100042, as set forth in item 6 of Paper 9. It is acknowledged that Applicant intends to address the propriety of the this rejection upon an indication that the application is otherwise in condition for allowance.

4. Claims 43, 44, 45, 47, 50 and 51 stand rejected and new claims 52, 54, 55, 57 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5284746 in view of

Kang, YS. et al. Mol. Cell. Biol. 10(2582-2590)1990, as set forth in item 8 of Paper 9 and reiterated below:

U.S. Patent No. 5284746 discloses a transformed yeast cell comprising a reporter gene (see col 12, L43, e.g. LacZ see col 12, L65-66) under the control of a pheromone-responsive promoter (see col 12, L42; e.g. FUS1 promoter see col 12, L48-56), a heterologous mammalian G-protein coupled receptor gene (β2- adrenergic receptor, for example, see col 1), wherein said receptor is a hybrid receptor comprising intracellular sequences from yeast and sequences from heterologous receptors (see col 3, L2), wherein said yeast receptor sequences are STE2 sequences (see col 4, L33), wherein said receptor is capable of inducing yeast pheromone response (see col 4, L5), each gene being under the control of a separate promoter (second construct) (see col 12, L 41), and a mutation in the ste2 gene causing increased sensitivity to receptor activation (see col 10, L8-9).

The disclosure of U.S. Patent No. 5284746 does not teach a hybrid Gα protein comprising yeast Gα nor an otherwise heterologous Gα protein. Kang, Y.S. et al. disclose heterologous yeast/mammalian hybrid Gα proteins expressed in yeast that complement the cell cycle arrest in cells lacking endogenous Gα (scg1 mutant cells) (see page 258, 3rd para). Conversely, U.S. Patent No. 5284746 teaches that heterologous hybrid yeast\ mammalian G-protein-coupled-receptors can induce cell cycle arrest in cells lacking the endogenous receptor (see col 4, line 25-35). Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made, with reasonable expectation of success, to use hybrid Gα proteins

instead of hybrid G-protein receptors in the assay disclosed in U.S. Patent No. 5284746. The motivation to do so was provided by Kang et al. who stated that portions of mammalian Gα proteins (Gαi) which bind to mammalian receptors but do not interact with yeast βγ subunits could be made to do so by expressing them as hybrid proteins containing yeast sequences (See table 2).

Applicant argues that the 5284746 does not teach or suggest an assay in which yeast cells express a heterologous G-protein receptor. Applicant argues that hybrid receptors are not heterologous receptors, and that such a distinction is set forth in the specification as well as in the prior art. This argument has been fully considered but not deemed persuasive. It is well established in the art of molecular biology, and, in particular, the art of mammalian protein expression in yeast, that "hybrid" mammalian G-protein coupled receptors are a subgenus of "heterologous" mammalian G-protein receptors, i.e., that hybrid receptors are necessarily heterologous receptors. Stedman's Medical Dictionary defines "heterologous" as (1) pertaining to cytologic or histologic elements occurring where they are not normally found. (2) Derived from an animal of a different species., see entry: Heterologous, Stedman's Medical Dictionary 27th Edition, 2000, Lippincott Williams and Wilkins. The hybrid receptor taught in example 5 of the 5284746 patent (referred to by Applicant) is derived from a human receptor, and it is expressed in yeast, wherein it is not normally found; this makes it a heterologous receptor. It also contains yeast sequences, and this makes it, also, a hybrid receptor. At page 9 of the instant specification, King et al., Science 250(121-123)1990 is cited as an example of heterologous

GPCR expression in yeast. King et al. indicate that their receptor has both human and yeast sequences (see page 121, middle column), which makes it a hybrid receptor. King et al. also refer to this receptor as a heterologous receptor (see page 123, last paragraph), as is consistent with the use of the term in the art, in the instant specification, and in the previous Office action. Regarding the use of these terms in the Kang article on page 2585 under the heading RESULTS, this appears to be simply a short-hand, as it is perhaps less confusing to say "expression of heterologous and hybrid Gα proteins in yeast", then to say "expression of heterologous proteins that are not hybrids, and hybrid Gα proteins in yeast" or "expression of hybrid and other heterologous proteins in yeast" which would be technically correct. The instant claims recite the term "heterologous G-protein coupled receptor" and so encompass hybrid receptors such as those of King et al. and of the 5284746 patent. It is agreed that the 5284746 patent exclusively teaches hybrid receptors in its assays, thus, it is suggested to Applicant that one way to obviate this rejection would be to add the limitation "wherein said G-protein coupled receptor is not a mammalian/yeast hybrid receptor". It should be noted, however, that such a limitation would raise enablement issues regarding the claims.

Both King et al and the Sledziewski patent (5284746) teach that heterologous mammalian G-protein coupled receptors can be made to work in the claimed assay systems if those receptors contain various portions of the yeast receptor. The examiner's proposed amendment would severely limit this genus to only those mammalian G-protein receptors that could work without yeast sequences, such receptors would have to both: a) be expressed sufficiently in a yeast cell

and b) couple to downstream effectors. The prior art is clear on the point that it is unpredictable which of the thousands of naturally occurring receptors can actually be used in this way, e.g. King *et al.* found that the β2-adrenergic receptor required a yeast leader sequence to be expressed to a sufficient level in yeast. The instant specification appears to acknowledge this problem at page 44, lines 25-34. The instant specification provides some guidance as to how to get heterologous receptors to couple to Gα by making chimeric Gα subunits, however, the examiner can find no teachings regarding making heterologous G-protein coupled receptors, that are not sufficiently expressed in yeast, to be sufficiently expressed without adding yeast sequences to them. Applicant provides only one example of a GPCR (C5a receptor) which can function, unadulterated, in the assay system. This example seems to be merely fortuitous, however, because the specification does not provide guidance as to how or why this is the case, nor guidance as to how to get other receptors to behave as fortuitously.

Therefore, the examiner's proposed amendments would introduce new issues regarding enablement for the claimed yeast cells. As the claims now stand, the claims are enabled for the broad scope of heterologous G-protein receptors expressed in yeast, of which, heterologous G-protein coupled receptors that are not mammalian/yeast hybrid receptors make up only a very small fraction. The examiner's proposed amendments would limit the claims to the genus of heterologous mammalian G-protein coupled receptors that do not include a coding sequence from a yeast G protein coupled receptor fused thereto. As discussed above, it does not appear that the guidance provided in the specification is commensurate with the scope of this genus.

Applicant appears to concede that the Kang hybrids do work as downstream effectors, however Applicant again argues that the hybrids do not couple to the yeast receptor, receptor binding being required for the claimed assay to work. This argument has been fully considered but not deemed persuasive. As discussed previously, Kang et al. demonstrate an intriguing property of yeast cells that had been suggested by other genetic experiments. It is the yeast Gβγ subunit and not the Gα subunit that is responsible for [downstream] signal transduction; this is in contrast to most animal systems wherein the Gα subunit couples to downstream effectors (see the DISCUSSION, especially the 2nd paragraph). Applicant appears to acknowledge this but argues that because the Kang hybrids did not bind to the yeast receptor, then one of ordinary skill in the art would not have recognized a suggestion to make hybrid Gα subunits that couple to mammalian receptors expressed in yeast. This argument has been fully considered but not deemed persuasive. The Kang hybrid Gα subunit complements growth arrest phenotype (i.e. it binds to yeast Gβγ), yet it does not bind to the yeast receptor (i.e. does not allow mating). Similarly, the wild-type rat Gα subunit complements growth arrest phenotype (i.e. it binds to yeast Gβγ), yet the rat Gα subunit does not bind to the yeast receptor (i.e. does not allow matting) (see the Kang Abstract). Thus, the rat Gα subunit and the hybrid have the same activities with respect to yeast receptor binding and interaction with the yeast Gβγ. Although neither the rat Gα subunit nor the hybrid subunit bind to yeast receptors, it is known, of course, that the rat Gα subunit <u>does</u> bind to mammalian receptors, thus one of ordinary skill in the art would not be dissuaded from using a hybrid Gα subunit to couple to mammalian receptors in

yeast, as Applicant asserts. To the contrary, at page 2588, col 2, 1st full paragraph, Kang et al. state: "These results indicate sufficient conservation of structure between yeast and mammalian Gα proteins to allow the function of appropriate domains in the hybrids and suggest that, like [rat] Gαs and Gαi, these hybrid proteins can interact with Gβγ but not with the pheromone receptors". Thus, Kang et al. provide both the suggestion and expectation of success to make a hybrid Gα subunit with the binding properties of rat Gα proteins.

5. Claims 46, 47, 48, 49 stand rejected and new claims 53 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5284746 and Kang, YS. et al. Mol. Cell. Biol. 10(2582-2590)1990 for the reasons put forth above regarding claims 43, 44, 45, 47, 50, 51, 52, 54, 55, 57 and 58 and in further view of Chang et al.. (Cell 63:999-1011,1990), as set forth in item 9 of Paper 9. Applicant's arguments regarding U.S. Patent No. 5284746 and Kang et al. have been addressed above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Fridays from 8:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

June 30, 2002

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
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